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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/031,532	05/02/2002	Harry B. Gray	CIIT1490-3	6210
	7590 10/05/2004		EXAMINER	
Lisa A Haile Gray Cary Ware & Friedenrich Suite 1100 4365 Executive Drive San Diego, CA 92121-2133			PADMANABHAN, KARTIC	
			ART UNIT	PAPER NUMBER
			1641	
DATE MAILED: 10/05/2004				

Please find below and/or attached an Office communication concerning this application or proceeding.

<b>Office Action Summary</b>	<b>Application No.</b> 10/031,532	<b>Applicant(s)</b> GRAY ET AL.	
	<b>Examiner</b> Kartic Padmanabhan	<b>Art Unit</b> 1641	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

#### Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

#### Status

- 1) ☒ Responsive to communication(s) filed on 29 July 2002.
- 2a) ☐ This action is **FINAL**.      2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

#### Disposition of Claims

- 4) ☒ Claim(s) 20-37 is/are pending in the application.
- 4a) Of the above claim(s) \_\_\_\_\_ is/are withdrawn from consideration.
- 5) ☐ Claim(s) \_\_\_\_\_ is/are allowed.
- 6) ☒ Claim(s) 20-37 is/are rejected.
- 7) ☐ Claim(s) \_\_\_\_\_ is/are objected to.
- 8) ☐ Claim(s) \_\_\_\_\_ are subject to restriction and/or election requirement.

#### Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on \_\_\_\_\_ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.  
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).  
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☒ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

#### Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All    b) ☐ Some \*    c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
  2. ☐ Certified copies of the priority documents have been received in Application No. \_\_\_\_\_.
  3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).
- \* See the attached detailed Office action for a list of the certified copies not received.

#### Attachment(s)

- |  |   |
|--|---|
| 1) <input checked="" type="checkbox"/> Notice of References Cited (PTO-892)  | 4) <input type="checkbox"/> Interview Summary (PTO-413)<br>Paper No(s)/Mail Date. _____ |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948)                                   | 5) <input type="checkbox"/> Notice of Informal Patent Application (PTO-152)             |
| 3) <input type="checkbox"/> Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08)<br>Paper No(s)/Mail Date _____ | 6) <input type="checkbox"/> Other: _____  |

## **DETAILED ACTION**

### ***Oath/Declaration***

1. The oath or declaration is defective. A new oath or declaration in compliance with 37 CFR 1.67(a) identifying this application by application number and filing date is required. See MPEP §§ 602.01 and 602.02.

The oath or declaration is defective because:

It does not state that the person making the oath or declaration acknowledges the duty to disclose to the Office all information known to the person to be material to patentability as defined in 37 CFR 1.56.

### ***Specification***

2. The lengthy specification has not been checked to the extent necessary to determine the presence of all possible minor errors. Applicant's cooperation is requested in correcting any errors of which applicant may become aware in the specification.

### ***Claim Rejections - 35 USC § 112***

3. The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

4. Claims 20-37 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.
5. Claim 20 is rejected under 35 U.S.C. 112, second paragraph, as being incomplete for omitting essential steps, such omission amounting to a gap between the steps. See MPEP

Art Unit: 1641

§ 2172.01. The omitted step is the way in which signal initiation occurs. Unless the signal is being emitted constantly, it needs to be activated or initiated in some way.

6. Claim 33 is rejected as vague and indefinite because it appears that applicant intends to recite Cytochrome P450, rather than 350.

7. Claims 35 and 36 are rejected as vague and indefinite because they rely on the Figures and cannot stand alone. Claims must be able to stand alone to comply with the requirements of Section 112 of Title 35 of the US Code.

8. Claim 37 is rejected under 35 U.S.C. 112, second paragraph, as being incomplete for omitting essential steps, such omission amounting to a gap between the steps. See MPEP

§ 2172.01. The omitted step is the way in which signal initiation occurs. Unless the signal is being emitted constantly, it needs to be activated or initiated in some way.

***Claim Rejections - 35 USC § 102***

9. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.

10. Claims 20-29, 31-34, and 37 are rejected under 35 U.S.C. 102(a) as being anticipated by Wilker et al. (Angew. Chem. Int. Ed. 1999). The reference discloses substrates for rapid delivery of electrons and holes to buried active sites in proteins. The reference discloses a photochemical method for this purpose by tethering a Ru photosensitizer to a protein substrate, which reduces the P450 heme very rapidly. By linking sensitizers to substrates, the reactive redox states in enzyme interiors can be studied more closely. The photosensitizer  $[\text{Ru}(\text{bpy})_3]^{2+}$  is linked through

Art Unit: 1641

a hydrocarbon chain to a species with high affinity for the P450 heme pocket (imidazole, adamantane, or ethylbenzene). Laser excitation of  $\text{Ru}^{11}\text{-Im}$  followed by reductive quenching yields a powerful reductant,  $\text{Ru}^1\text{-Im}$ . In the presence of P450, the reductant is converted rapidly to  $\text{Ru}^{11}\text{-Im}$ . This oxidation occurs at the same time as reduction of the heme group. The use of sensitizer-linked substrates allows the preparation of new oxidized and reduced states of P450.

11. Claims 20-29, 31-34, and 37 are rejected under 35 U.S.C. 102(a) as being anticipated by Wilker et al. (Book of Abstracts, 1998). The reference discloses sensitizer-linked substrates for the rapid delivery of electrons and holes to protein active sites. Photosensitizers such as  $[\text{Ru}(\text{bpy})_3]^{2+}$  are derivatized with hydrocarbon chains terminating in protein substrates. Binding of these sensitizer-substrate conjugates to the protein provides an efficient, covalent pathway for mediating electron transfer between the photosensitizer and the protein active site. The methods involve heme oxygenase cytochrome P450cam,  $[\text{Ru}(\text{bpy})_3]^{2+}$ , the protein substrates ethylbenzene, adamantane, and imidazole. The synthesis and protein binding properties of  $\text{Ru}-(\text{CH}_2)_{11}\text{-EB}$ ,  $\text{Ru}-(\text{CH}_2)_{11}\text{-Ad}$  and  $\text{Ru}-(\text{CH}_2)_{13}\text{-Im}$  are also described. Flash photolysis techniques are employed to generate strongly oxidizing  $\text{Ru}(\text{III})$  or reducing  $\text{Ru}(\text{I})$  derivatives transiently. The buried heme of P450cam has been oxidized and reduced with the method of the reference.

12. Claims 20-29, 31-34, and 37 are rejected under 35 U.S.C. 102(a) as being anticipated by Dmochowski et al. (Book of Abstracts, 1998). The reference discloses techniques to rapidly inject electrons and holes into the active site of cytochrome P 450 in an effort to generate and characterize reactive intermediates of this ubiquitous heme oxygenase. Photosensitizers such as  $[\text{Ru}(\text{bpy})_3]^{2+}$  are covalently attached to hydrocarbon chains terminating in protein substrates.

Art Unit: 1641

Binding of these sensitizer-linked substrates creates a direct, covalent pathway that mediates efficient electron transfer between the ruthenium and the heme. Initial experiments involve the Ru-tethered protein substrates ethylbenzene, adamantane, and imidazole. The synthesis and protein binding of these sensitizer-substrate conjugates are also described. Laser photoexcitation of the sensitizer, followed by oxidative or reductive quenching of the excited state, generates oxidizing Ru(III) or reducing "Ru(I)" derivatives transiently. By these rapid, active-site-directed methods, the oxidation and reduction of the cytochrome P 450 heme has been demonstrated.

13. Claims 20-29, 31-33, and 37 are rejected under 35 U.S.C. 102(a) as being anticipated by Wilker et al. (Book of Abstracts, 1999). The reference discloses techniques to generate and observe enzyme intermediates in buried active sites. Protein binding of the substrate moiety creates a covalent pathway to mediate efficient electron and hole transfer between the  $[\text{Ru}(\text{bpy})_3]^{2+}$  photosensitizer and enzyme active site. By applying this strategy of linking protein substrates and photosensitizers, the heme of cytochrome P450cam in two redox states is shown.

***Claim Rejections - 35 USC § 103***

14. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

15. The factual inquiries set forth in *Graham v. John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.

Art Unit: 1641

2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

16. This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

17. Claims 30 and 35-36 are rejected under 35 U.S.C. 103(a) as being unpatentable over Wilker et al. (Angew. Chem. Int. Ed. 1999), Wilker et al. (Book of Abstracts, 1998), Dmochowski et al. (Book of Abstracts, 1998), or Wilker et al. (Book of Abstracts, 1999) in view of Chrespi et al. (US Pat. 5,726,041).

The Wilker and Dmochowski references teach methods of delivering electrons and holes to buried active sites in proteins. However, none of the references teach the use of coumarin as the photosensitizer.

Chrespi et al. teach methods of detection, wherein coumarin is a substrate for cytochrome P450.

It would have been prima facie obvious to use a coumarin compound as the photosensitizer with the methods of the Wilker or Dmochowski references because Chrespi teaches that coumarin is a suitable substrate for P450. As such, one would have had a reasonable expectation

Art Unit: 1641

of success in substituting a coumarin compound for  $[\text{Ru}(\text{bpy})_3]^{2+}$  as the photosensitizer with the methods of Wilker or Dmochowski.

**Conclusion**

Claims 20-37 are rejected.

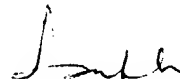
Any inquiry concerning this communication or earlier communications from the examiner should be directed to Kartic Padmanabhan whose telephone number is 571-272-0825. The examiner can normally be reached on M-F (8:30-5:00).

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Long Le can be reached on 571-272-0823. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Kartic Padmanabhan  
Patent Examiner  
Art Unit 1641

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LONG V. LE  
SUPERVISORY PATENT EXAMINER  
TECHNOLOGY CENTER 1600

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